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ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/688,821	WICKSTROM ET AL.	
	Examiner	Art Unit	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,7-14,16,26-34,41-45,48-52,54-56,69-73,75,80,82,83,86 and 88-101* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07/27/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1,3,4,7-14,16,26-34,41-45,48-52,54-56,69-73,75,80,82,83,86 and 88-101.

DETAILED ACTION

1. Claims 2, 5, 6, 15, 17-25, 35-40, 46, 47, 53, 57-68, 74, 76-79, 81, 84, 85, and 87 have been cancelled. Claims 1, 3, 16, 88 and 89 have been amended.

Claims 1, 3, 4, 7-14, 16, 26-34, 41-45, 48-52, 54-56, 69-73, 75, 80, 82, 83, 86, and 88-101 are pending and under examination.

2. The rejection of claims 1, 3, 4, 7-14, 16, 26-34, 41-45, 48-52, 54-56, 69-73, 75, 80-83, 86, and 88-101 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn in response to Applicant's amendments filed on 07/27/2009.

The rejection of claims 1, 3, 4, 7-14, 16, 26-34, 41-45, 48-52, 54-56, 69-73, 75, 80-83, 86, and 88-101 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in response to Applicant's amendments filed on 07/27/2009.

Response to Arguments

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1, 3, 4, 7-14, 16, 26-31, 34, 41-45, 48, 50, 52, 54-56, 69-73, 75, 80, 83, 86, and 88-101 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Tomalia et al. (US Patent No. 5,714,166), in view of both Basu et al. (Bioconjugate Chem, 1997, 8: 481-488) and Meade et al. (US Patent No. 6,713,046).

Tomalia et al. teach a compound having the formula T-P-M, wherein P represents a dendrimer such as PMAM (i.e., polymeric diagnostic or therapeutic moiety, which is a branched oligomeric polychelant) or Starburst, M represents a carried material such as PNA, T represents a targeting moiety that can be an antibody fragment such as Fab, Fab', and wherein M and T are associated with the dendrimer via the same or different linkers (i.e., covalent bond); the linkers could be cleavable (claims 1, 4, 7-10, 34, 88, 89, and 99-101) (column 1, lines 45-50, column 2, lines 53-65, column 16, lines 31-52, column 22, lines 15-35, column 47, lines 1-10, column 52, lines 57-60). Tomalia et al. teach that two or more dendrimers can be associated with each other (covalently bridged or through other associations) (claim 12) and that the dendrimers can comprise chelants, i.e., the diagnostic moiety comprises a plurality of chelants, wherein the chelants can be complexed with diagnostic metal ions (claims 13 and 26) (column 3, lines 22-40, column 13, lines 5-11, column 19, lines 11-16, column 22, lines 1-29, column 45, lines 1-9,) and optionally can comprise additional agents that could be diagnostic metal ions, such as gadolinium (claims 4, 13, 14, 16, and 54) (column 1, lines 59-65, column 22, lines 15-35, column 88, Example 24, column 89, Table XI). Tomalia et al. teach that the compound can be used either *in vitro* or *in vivo* as a cancer therapeutic and diagnostic agents for noninvasive imaging and for transferring of

genetic material, such as PNA into cells to block the production of specific proteins, i.e., Tomalia et al. teach a method of retaining a compound inside the cells for diagnostic or therapeutic purposes (claims 41-45, 48, 52, 69, 70, 73, 75, 90, 91) (column 28, lines 28-40, column 39, lines 25-30, column 54, lines 8-18, claim 32). For *in vivo* use, the compound can be administered into the portal vein, i.e., intravascular administration (claims 55 and 56) (column 54, lines 10-15). With respect to the limitation recited in claim 28, PNAs comprise N-ethylaminoglycine backbone units and the bases are covalently bound to the backbone by methylene-carbonyl units (see Basu et al.). With respect to the limitation of pharmaceutical composition, the transfection buffer (i.e., a pharmaceutically acceptable carrier) comprising the conjugate is a pharmaceutical composition (claims 83, 86, and 92). With respect to the specific linkers and their length (claims 1, 3, 88, 89, and 93-98), the specific chelants (claims 26 and 27), or the specific PNA lengths (claim 29), absent evidence of unexpected results, if the general conditions of a given method are disclosed in the prior art, it would have been obvious to the ordinary skilled artisan to vary the parameters in a given method (in the instant case, the linkers or the chelants) with the purpose of optimizing the results. Again, absent evidence to the contrary, it is generally not inventive to discover the optimal working conditions of a prior art method, such conditions can be identified by routine experimentation. With respect to the limitations of the of the target nucleic acid sequence comprising some or all of a consecutive sequence of bases in a RNA transcript and of the RNA transcript being heteronuclear or messenger RNA (claims 30, 31, 50, 51, 71, 72, and 80), these are inherent to a method using PNA. It is noted that

Tomalia et al. do not teach the specific arrangement X-L1-P-L2-T recited in the instant claims. However, Tomalia et al. teach all components necessary for this arrangement. It is noted that there is no evidence on the record that the claimed arrangements result in a compound exhibiting an unexpected property. The arrangement is not significant if it does not provide a novel feature. Moreover, it would have been obvious to the ordinary skilled artisan to vary the arrangement, with the purpose to achieve the optimum control of targeted delivery to a particular cell/site. Absent evidence to the contrary, it is generally not inventive to discover the optimal working conditions of a prior art method, such conditions can be identified by routine experimentation.

Although Tomalia et al. teach cleavable linkers, they do not specifically teach a biodegradation cleavage site. Meade et al. teach a biodegradation cleavage site (claim 11) (column 14, lines 20-30). It would have been obvious to one of skill in the art, at the time the invention was made, to include a biodegradation cleavage site, as taught by Meade et al, with a reasonable expectation of success. The motivation to do so is provided by Meade et al. who teach that such a site allows the drug (in the instant case, the PNA) to freely interact with its target. One of skill in the art would have been expected to have a reasonable expectation of success because Meade et al. teach the successful use of such sites.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant traversed the instant rejection on the grounds that Tomalia et al. specifically restricted "genetic materials" (which include PNA) as belonging to a class for which "formation of the complex does not take place via covalent bonding" ('166 Tomalia at column 47, lines 55-62). The other recitations of the (T)e*(P)x*(M)y structure (column 2, lines 53-65, column 16, lines 31-52, column 22, lines 15-35, column 47, lines 1-10, column 52, lines 57-60) do not teach that M represents a PNA. At no point in the 5,714,166 patent do Tomalia et al. state that PNA, or any genetic material, can be covalently bonded to a dendrimer, not in the claims, not in the background, not in the examples. Therefore, Tomalia et al. teach away from covalent bonding of genetic materials to dendrimers.

In contrast to the instant claims, Tomalia et al. actually teach a compound with the formula (T)e*(P)x*(M)y (column 16, lines 37-52), (column 18, lines 23-67), (column 19, lines 1-67), (column 20, lines 1-29), (column 22, lines 20-26), wherein M represents a diagnostic or therapeutic agent, such as a radionuclide, T represents a target director, such as a moiety that can bind a cell-surface molecule, or a PNA that can bind a nucleic acid, P represents a dendrimer, and wherein M and T are associated with P via identical or different bonds. The instant claims, which are directed to a compound X-L1-P-L2-T, wherein X represents a diagnostic or therapeutic agent, such as a radionuclide chelated to a dendrimer (comparable to P*M in Tomalia et al.), P represents a PNA that can bind a nucleic acid (comparable to T in Tomalia et al.), and T represents a cell surface target director, such as a moiety that can bind a cell-surface molecule (comparable to T in Tomalia et al.), and wherein X, P and T are associated with identical or different spacers

L1 and L2 to prevent steric hindrance. The L1 and L2 spacers are a non-obvious solution, not taught or suggested by Tomalia et al., or the combination of the references, to the problem of steric hindrance between the three functional units of the claimed compound. In addition, the claims are directed to spacers of from 10Å - 30Å, which is not taught or suggested in the Tomalia reference.

Applicant argues that, if the Examiner argues that Basu and Meade do not have anything to remedy in Tomalia, it is unclear why they were cited.

However, Applicant argues, the deficiencies in the Tomalia reverences are not cured by the Basu or Meade references. Basu et al. reported a construct of the form P-L2-T designed to bind to a specific cellular receptor, internalize to the cytoplasm, and bind to its specific target mRNA. The construct as disclosed in the Basu reference does not contain a diagnostic or therapeutic moiety (X) covalently conjugated to at least one PNA (P) and covalently conjugated to at least one targeting moiety (T) that selectively binds to a cell surface receptor, and does not contain a spacer L1. One skilled in the art would therefore not have been motivated by Basu et al. to covalently bond X-L1 to P-L2-T. Additionally, as noted above, Tomalia et al. teach away from covalent bonding of genetic materials to dendrimers.

Applicant argues that Meade et al. do not disclose utilizing PNA covalently bound to a dendrimer and or targeting messenger RNA in a cell. Meade only taught that water access to a Gd(III) reporter for MRI could be achieved by biodegradation of a protecting peptide strip over the top of a chelator binding the Gd(III). Moreover, it would not be obvious to a person skilled in the art to modify the teachings of Tomalia with Meade and

Basu to reach all the limitations of the claims, for the reasons set forth in the Declaration of Dr. Eric Wickstrom.

Applicant has previously submitted a Declaration under 37 CFR § 1.132 of Dr. Eric Wickstrom, submitted December 19, 2007. Here, the Examiner attempts to argue that Tomalia can be modified with the Meade and Basu patents to teach or suggest the claimed invention. However, this modification would be unsatisfactory for its intended purpose, as demonstrated by the unsuccessful attempt by Applicant to synthesize a functional compound as claimed using the teachings or suggestions of Tomalia. In fact, Applicant had to completely alter the approach to synthesize the instantly claimed compound (Declaration at paragraphs 13-17). Here, if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious. See *In re* Ratti, 270 F.2d 810 (CCPA 1959). This is shown here. However, as shown in the Declaration, Applicants' attempt to use the teachings of Tomalia to reach the claimed invention was unsuccessful, thereby showing that it would require a substantial reconstruction and redesign of the elements shown in the primary reference as well as a change in the basic principle under which the primary reference construction was designed to operate, as in the *In re* Ratti case, therefore the claims are patentable.

In addition, while obviousness does not require absolute predictability, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness, see *In re*

Rinehart, 531 F.2d 1048 (CCPA 1976), MPEP 2143.02. Here, Applicants attempted to use the Tomalia teachings as the basis for reaching the claimed invention, but were unsuccessful, thereby showing that there was no reasonable expectation of success in modifying the Tomalia teachings. Therefore, the evidence provided by Applicant demonstrates that Applicant has attempted to utilize the PAMAM dendrimer according to the teachings of Tomalia, and that this attempt was unsuccessful.

The Examiner cites Goh et al. who allegedly teach solid-phase synthesis of covalent dendrimer-oligonucleotide conjugates by linking dendrimers to oligonucleotides attached to solid supports (p. 2954 and 2955). Additionally, Basu et al. teach solid phase synthesis of targeting ligand-PNA conjugates, wherein the targeting ligand is automatically synthesized on a solid support, followed by the assembly of the PNA. The Examiner concludes that by reading Basu et al. and Goh et al., one of skill in the art would know how to successfully extend a dendrimer from a solid phase-attached ligand-PNA.

However, Goh et al. teach extension of ester-linked dendrimers from the termini of normal DNA oligonucleotides. But blood and cells contain significant concentrations of nucleases and esterases. Those skilled in the art are aware that normal DNA is rapidly degraded in blood and cells by nucleases. Thus, designers of DNA analogs for administration to animals and humans are aware of the need to create derivatives that resist nucleases. Those skilled in the art are aware that ester linkages are rapidly degraded in blood and cells by nonspecific esterases. Thus, designers of dendrimers for administration to animals and humans are aware of the need to create derivatives

that resist esterases. As a result, Goh et al. teach away from the composition of matter in the instant application, which depends on DNA analogs with amide linkages that are resistant to nucleases, and dendrimers with amide linkages that are resistant to esterases. Therefore, one of skill in the art would not consider application of the methods of Goh et al. to prepare agents for imaging or therapy in animals or humans.

Therefore, the evidence provided by Applicant demonstrates that Applicant has attempted to utilize the PAMAM dendrimer according to the teachings of Tomalia, and that this attempt was unsuccessful.

In addition, Applicant has recently had a Small Business Innovation Research (SBIR) grant, (Pak, Koon Y, SBIR Phase I FT R44CAt36306-01, Radiohybridization Imaging of HER2 Oncogene to Detect Breast Cancer, 2008, copy attached, and cited on the IDS submitted herewith), funded by the United States National Institutes of Health. The Small Business Innovation Research (SBIR) program is a program for domestic small business concerns to engage in Research/Research and Development (R/R&D) that has the potential for commercialization.

Applicant has designed and demonstrated a novel technology to see visualize hyperactive cancer genes from outside the body, which is called radiohybridization imaging (RHI). RHI scans the entire organ or body to find all sites of cancer gene activation, whether or not a lump has formed. RHI probes are peptide nucleic acid (PNA) sequences that hybridize specifically to messenger RNAs (mRNAs) copied from activated cancer genes. Applicant added a small peptide analog to allow the RHI probes to be taken up by breast cancer cells. Finally, Applicant chelated radionuclides

to permit external imaging by positron emission tomography (PET) scanning. RHI probes for CCND1, IRS1, MYCC, and KRAS mRNAs, injected into animal models, enabled the visualization of breast cancer, pancreas cancer, and prostate cancer xenografts. High levels of human epidermal growth factor receptor 2 (Her2) protein are associated with aggressive, invasive, estrogen-independent breast cancers.

In the Grant Application, Applicant has demonstrated that [99mTc]peptide-PNA probes do not provide tumor images without an IGF1 analog, or without a complementary PNA. However, specific imaging of MYCC mRNA expression in MCF7:IGF1R breast cancer xenografts was observed with a specific [99mTc]peptide-MYCC PNAIGF1 analog. The probes are not rapidly metabolized into fragments. These results demonstrate imaging of oncogene expression in vivo with [99mTc]chelator-PNA-IGF1 analogs (see Figures 4-6). Applicant has demonstrated that CCND1 cancer gene activity in ER+ xenografts can be detected specifically from outside the body by probing with [99mTc]chelator-PNA-IGF1 analog chimeras (see Figures 7-12). Applicant has demonstrated the preparation of PET probes for CCND1 mRNA, and image those mRNAs in human BT474 Her2+ breast cancer xenografts in immunocompromised mice. This is a stringent test, because CCND1 mRNAs are not expressed as strongly in Her2+ breast cancer xenografts as they are in Her2- breast cancer xenografts, like the MCF7 xenografts they have already imaged successfully. These PET imaging results represent a rational basis for malignancy classification targeted to CCND1 mRNA, depending on their expression levels revealed by imaging (see Figures 13-17). Applicant has demonstrated that CCND1 PET radiohybridization probes can identify

sites of CCND1 overexpression in sporadic breast lesions, as opposed to normal mammary tissue (see Figure 18). This system is the closest possible model for the clinical situation. Furthermore, NIH has demonstrated confidence that the Applicant and industrial partners can accomplish a similar goal for HER2 overexpression and develop a clinically useful radiodiagnostic.

Therefore, all the limitations of the claims are not taught or suggested in the combination of the Tomalia, Meade, and Basu references. Accordingly, Applicant requests reconsideration and withdrawal of the rejection.

Applicant's arguments are acknowledged; however, they are not found persuasive for the following reasons:

Most of the Applicant's arguments are not new and were previously addressed. Only the new arguments are addressed below.

Applicant argues that, since the Examiner states that Basu and Meade do not have anything to remedy in Tomalia et al., it is not clear why the references were cited. The Examiner made this statement because, since Tomalia et al. teach non-covalent binding of DNA to dendrimers, there is nothing to be cured regarding this limitation, as Applicant argues. Applicant is well aware that Basu and Meade were cited for teaching claim limitations other than the non-covalently coupling of DNA to dendrimers. Had Tomalia et al. taught all claim limitations, this would have been anticipation and not an obviousness-type rejection, in which case citing Basu and Meade would have been unnecessary. However, the instant rejection is an obviousness-type rejection;

therefore, citing Basu and Meade for teaching limitations not disclosed by Tomalia et al. is proper.

Applicant argues that, since Basu et al. teach a construct in the form of P-L2-T (i.e., a construct which does not contain a diagnostic or therapeutic moiety), one of skill in the art would not have been motivated by Basu et al. to covalently attach X-L1 to the P-L2-T of Basu et al. Not only is this argument not supported by any evidence, but it is also irrelevant to the instant rejection which is not based on modifying Basu et al. This reference was cited to evidence that having N-ethylaminoglycine backbone units and bases covalently bound to the backbone units by methylene-carbonyl groups (as recited in the instant claim 28) is inherent to PNAs.

Applicant argues that Goh et al. teach away from the instant composition, which depends on DNA analogs with amide linkages that are resistant to nucleases, and dendrimers with amide linkages that are resistant to esterases. First, it is noted that Goh et al. was not used to reject the claims. The reference was cited in response to Applicant's argument that, at the time the invention was made, coupling DNA to dendrimers would have been within the knowledge and capabilities of one of skill in the art (see the non-final Office action mailed on 02/25/2009). Second, the cited prior art teaches PNA (i.e., DNA analogs with amide linkages that are resistant to nucleases). Third, the claims and the specification do not exclude biodegradable linkages such as ester linkages; in fact, the instant specification teaches the desirability of using biodegradable ester and amide linkages (note that the specification teaches that amide linkage is biodegradable) (see claim 11 and the specification, p. 13, lines 25 and 26, p.

14, lines 10-14). And even assuming that the claims would exclude ester linkages, attaching DNA via linkages other than ester linkages was routine in the prior art. The instant specification does not teach more than this (see the instant specification, p. 17, lines 12-18).

Furthermore, having an SBIR grant does not render the claimed invention non-obvious over the prior art.

For the reasons set forth above, Applicant's arguments are not found persuasive and the rejection is maintained.

5. Claims 1, 3, 4, 7-14, 16, 26-34, 41-45, 48, 49-52, 54-56, 69-73, 75, 80, 82, 83, 86, and 88-92 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Tomalia et al., taken with both Meade et al. and Basu et al., in further view of Nakano et al. (Molecular Therapy, 2001, 3: 491-499).

The teachings of Tomalia et al., Meade et al., and Basu et al. are applied as above for claims 1, 3, 4, 7-14, 16, 26-31, 34, 41-45, 48, 50, 52, 54-56, 69-73, 75, 80, 83, 86, and 88-92. Tomalia et al., Meade et al., and Basu et al. do not teach an oncogene, wherein the oncogene is K-RAS (claims 32, 33, 72, and 82), nor do they specifically teach treating pancreatic cancer (claim 49). Nakano et al. teach gene therapy by using antisense K-*ras* as a therapeutic agent for cancer (Abstract, p. 492, column 1, last paragraph, p. 493 bridging p. 495). It would have been obvious to one of skill in the art, at the time the invention was made, to use the compound and the method of Tomalia et al., Meade et al., and Basu et al., wherein the PNA is directed against K-*ras*, to deliver

diagnostic and therapeutic agents to cancer cells such as colon and pancreatic cancer cells that are known to over-express K-*ras*, with a reasonable expectation of success. Such a delivery of a diagnostic agent would result in detecting the over-expression of K-*ras* transcript inside these cells. One of skill in the art would have been motivated to do so because Nakano et al. teach that K-*ras* is over-expressed in many cancer cells. One of skill in the art would have been expected to have a reasonable expectation of success because the art teaches the successful use of such methods. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant traversed the instant rejection on the grounds that Nakano et al. do not cure the deficiencies of Tomalia et al., Meade et al., and Basu et al. The rejection is maintained because Tomalia et al., Meade et al., and Basu et al. do teach the claimed invention for the reasons set forth above.

6. Claims 1, 3, 4, 28-32, 34, 41, 42, 48-52, 69, 71-73, 75, 80, 83, 86, and 89-97 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Lewis et al. (Bioconjugate Chem, 2002, 13: 1176-1180), in view of Basu et al.

Lewis et al. teach a DOTA-PNA conjugate designed to target *bcl-2* (i.e., an oncogene), wherein DOTA comprises a radiometal (i.e., a polymeric diagnostic moiety) and wherein the PNA, which is 18 bases long, is further coupled to a peptide designated for intracellular delivery of the radiolabeled PNA (i.e., a targeting moiety); the targeting peptide and DOTA are conjugated to PNA via linkers (claims 1, 3, 4, 29, 31, 32, 34, 51,

52, 72, 73, 83, 86, and 89-97) (Abstract, p. 1177, Fig. 1). Lewis et al. teach contacting cells known to comprise high and low levels of *bcl-2* with the DOTA-PNA-peptide conjugate, allowing for the conjugate to be internalized by the cells, and detecting the conjugate within the cells to determine the level of expression of *bcl-2* transcript (claims 1, 30-32, 69, 71, 72, 80). Lewis et al. teach that cells expressing high levels of *bcl-2* internalize significantly more conjugate as compared to cells expressing low *bcl-2* levels, i.e., the presence of the conjugate inside the cells indicates over-expression of the *bcl-2* transcript therefore a pathological state that is cancer (claims 41, 42, 48-51, 75, and 80) (p. 1178, column 2 bridging p. 1179). It is noted that Lewis et al. do not teach the specific arrangement recited in the instant claims, i.e., X-L1-P-L2-T. However, Lewis et al. teach all components necessary for this arrangement. It is also noted that there is no evidence on the record that the claimed arrangements result in a compound exhibiting an unexpected property. The arrangement is not significant if it does not provide a novel feature. Moreover, it would have been obvious to the ordinary skilled artisan to vary the arrangement, with the purpose to achieve the optimum control of targeted delivery to a particular cell/site. Absent evidence to the contrary, it is generally not inventive to discover the optimal working conditions of a prior art method, such conditions can be identified by routine experimentation.

Lewis et al. do not teach a targeting moiety capable of binding to a cell surface molecule (claims 1, 41, 89, and 90). Basu et al. teach enhancing PNA delivery to cells by receptor-mediated endocytosis via coupling the PNA to ligands for cell surface receptors (Abstract; p. 481, columns 1 and 2; p. 482, column 1; p. 487, column 1, last

paragraph). Therefore, it would have been obvious to one of skill in the art, at the time the invention was made, to modify the composition of Lewis et al. by replacing their peptide with the ligand of Basu et al. to achieve the predictable result of obtaining a composition suitable for the intracellular delivery of nucleic acids. With respect to the limitation recited in claim 28, PNAs comprise N-ethylaminoglycine backbone units and the bases are covalently bound to the backbone by methylene-carbonyl units (see Basu et al.). With respect to the limitation of pharmaceutical composition (claims 83, 85, 86, and 92), the transfection buffer comprising the conjugate is a pharmaceutical composition. With respect to the specific linkers and their length (claims 1, 3, 88, 89, and 93-98), absent evidence of unexpected results, if the general conditions of a given method are disclosed in the prior art, it would have been obvious to the ordinary skilled artisan to vary the parameters in a given method with the purpose of optimizing the results. Again, absent evidence to the contrary, it is generally not inventive to discover the optimal working conditions of a prior art method, such conditions can be identified by routine experimentation. With respect to the limitations of the of the target nucleic acid sequence comprising some or all of a consecutive sequence of bases in a RNA transcript and of the RNA transcript being heteronuclear or messenger RNA (claims 30, 31, 50, 51, 71, 72, and 80), these are inherent to a method using PNA.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant traversed the instant rejection on the grounds that the Examiner's statement that one of skill in the art would know that the DOTA of Lewis et al. could substitute for polyethyleneimine, since both are known in the art to be efficient at delivery of nucleic acids to the cells is a serious error. DOTA is not comparable to polyethyleneimine in any aspect. DOTA is a small, negatively charged cyclic molecule designed to bind positively charged metal ions. DOTA has no ability to facilitate DNA uptake into any cell. Polyethyleneimine is a large positively charged detergent polymer that is designed to bind negatively charged polymers, like DNA, for the purpose of creating a neutral particle capable of facile cell penetration.

Lewis et al. teach a DOTA-PNA conjugate designed to target bcl-2 (i.e., an oncogene), wherein DOTA comprises a chelator for radiometal cations (i.e., a non-polymeric diagnostic moiety) and wherein the PNA, which is 18 bases long, and is further coupled to a detergent-like PTD-4 peptide that facilitates intracellular delivery of the radiolabeled PNA (i.e., a targeting moiety) into any cell. The detergent-like PTD-4 peptide and DOTA are conjugated to PNA via linkers (Abstract, p. 1177, Fig. 1). The Examiner improperly equates a peptide detergent intended for universal intracellular delivery of the radiolabeled PNA (i.e., a membrane permeating peptide PTD-4) with a specific cell surface receptor targeting moiety of the present invention, which is defined in the specification on page 21, lines 20-21 as "a moiety that comprises any chemical substance that is capable of binding to a cell surface molecule or being bound by a cell surface molecule (e.g., a receptor)." In the instant claims, targeting the conjugate of the invention to a cell surface receptor so that the internalization is achieved via a receptor

provides the desired specificity. This specificity cannot be achieved when a general membrane permeating peptide is used instead of a particular cell surface receptor ligand. Therefore, the membrane permeating peptide PTD-4 in Lewis et al. does not constitute a "targeting moiety" as contemplated in this invention.

With respect to the Examiner's statement that the use of linkers to inhibit steric hindrance between in PNA construct is taught by Tomalia et al., Applicant argues that the Examiner erroneously equates a short bifunctional linker intended only to connect the components of (T)e*(P)x*(M)y, with the instantly claimed flexible, hydrophilic spacer, L, 10-30 Å long, in X-L1-P-L2-T, intended to prevent functional interference between the PNA, P, and the moieties, X and T, attached to either end. Such spacers have only been introduced into such PNA constructs by the Applicant, as shown in their published papers. Any other use of such spacers to separate PNA from peptides or reporters appeared later, in imitation of Applicant's published strategy. Accordingly, the combination of the references does not teach or suggest all the claim limitations as asserted by the Examiner.

In addition, the claims are directed to a compound comprising a polymeric diagnostic or therapeutic moiety (X) covalently conjugated to at least one PNA (P) and covalently conjugated to at least one targeting moiety (T) that selectively binds to a cell surface receptor, wherein the PNA comprises a base sequence that is complementary to a target nucleic acid sequence, or pharmaceutically acceptable salts thereof. While the Basu reference discloses an IGF1 moiety, there is no teaching or suggestion of a diagnostic or therapeutic moiety (X) covalently conjugated to at least one PNA (P) and

covalently conjugated to at least one targeting moiety (T) that selectively binds to a cell surface receptor.

Accordingly, Applicant requests the withdrawal and reconsideration of the rejection.

Applicant's arguments are acknowledged; however the rejection is maintained for the following reasons:

None of the Applicant's arguments addresses the combination of Lewis et al. and Basu et al. In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). None of the references has to teach each and every claim limitation. If they did, this would have been anticipation and not an obviousness-type rejection. For these reasons, Applicant's arguments attacking Lewis et al. and Basu et al. individually are not found persuasive.

Applicant argues that the Examiner's statement that the DOTA of Lewis et al. could substitute for polyethyleneimine (PEI) is a serious error. It is not clear why Applicant argues such, since the Examiner never proposed replacing DOTA with PEI. The word PEI does not even appear in the rejection. Applicant also states that PEI and the PTD-4 peptide are detergents. This is incorrect, neither PEI nor the peptide is a detergent.

Applicant argues that the Examiner erroneously equates the short bifunctional linkers of Tomalia et al. with the instantly claimed flexible, hydrophilic spacer. This is incorrect. First, Tomalia et al. do not teach their linkers are all short. Second, the claims clearly encompass short linkers such as $(Gly)_4$ (see claim 3).

Applicant argues that the claimed linkers have only been introduced into PNA constructs by the Applicant, as shown in their published papers. This argument is not new and was previously addressed. Although Applicant argues that the claimed linkers have only been introduced into the PNA constructs by the Applicant, this is not supported by any evidence. The mere disclosure in published papers does not mean that the linkers were not known and used in the prior art. The prior art teaches obtaining compositions similar to the instant composition by using the linkers recited in claims 1 and 3, for example 5-30 Å long aliphatic chains or PEG comprising 2 to 100 recurring ethylene oxide units and reactive moieties (see WO 98/18496, p. 25, 35 and 36; incorporated by reference in the instant specification). Clearly, at the time the invention was made, using these linkers would have been within the capabilities of one of skill in the art.

Therefore, the combination of the references renders the claimed invention *prima facie* obvious and the rejection is maintained.

7. Claims 1, 3, 4, 28-34, 41, 42, 48-52, 69, 71-73, 75, 80, 82, 83, 86, and 89-97 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lewis et al. taken with Basu et al., in further view of Nakano et al.

The teachings of Lewis et al. and Basu et al. are applied as above for claims 1, 3, 4, 28-32, 34, 41, 42, 48-52, 69, 71-73, 75, 80, 83, 86, and 89-97. Lewis et al. and Basu et al. do not teach K-RAS (claims 33 and 82). Nakano et al. teach gene transfer antisense K-*ras* as a therapeutic agent for cancer (Abstract, p. 492, column 1, last paragraph, p. 493 bridging p. 495). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the compound of Lewis et al. and Basu et al. by using a PNA directed against K-*ras* and use it in a method of delivering diagnostic and therapeutic agents to cancer cells over-expressing K-*ras*, such as colon and pancreatic cancer cells, with a reasonable expectation of success. Such a delivery of a diagnostic agent would result in detecting the over-expression of K-*ras* transcript inside these cells. One of skill in the art would have been motivated to do so because Nakano et al. teach that K-*ras* is over-expressed in many cancer cells, including pancreatic cancer cells. One of skill in the art would have been expected to have a reasonable expectation of success because the art teaches the successful use of such methods. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant argues that Nakano et al. do not cure the deficiencies noted above. This is not found persuasive for the reasons set forth above.

8. Claims 1, 3, 4, 7-14, 16, 26-32, 34, 41-45, 48-52, 54-56, 69-73, 80, 83, 86, and 88-101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lewis et al. taken with Basu et al., in further view of both Tomalia et al. and Meade et al.

The teachings of Lewis et al. and Basu et al. are applied as above for claims 1, 3, 4, 28-32, 34, 41, 42, 48-52, 69, 71-73, 75, 80, 83, 86, and 88-97. The teachings of Tomalia et al. and Meade et al. are applied as above for claims 1, 3, 4, 7-14, 16, 26-31, 34, 41-45, 48, 50, 52, 54-56, 69-73, 75, 80, 83, 85, 86, and 88-92. Lewis et al. and Basu et al. do not teach a dendrimer or a plurality of chelants optionally complexed to one or more diagnostic metal ions, a biodegradation cleavage site, or intravascular administration (claims 7-14, 16, 26, 27, 43-45, 54-56, and 88). Tomalia et al. and Meade et al. teach these limitations (see above). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Lewis et al. and Basu et al. according to the teachings of Tomalia et al. and Meade et al., with a reasonable expectation of success. One of skill in the art would have been motivated to use the dendrimers of Tomalia et al. because the art teaches dendrimers as being very efficient in delivering agents to cells. The motivation to use a plurality of chelants is also provided by Tomalia et al., who teach that such compounds can be used to deliver multiple agents to cells. The motivation to use a biodegradation cleavage site is provided by Meade et al. who teach that such a site allows the drug (in the instant case, the PNA) to freely interact with its target. The limitation of intravascular administration is not innovative over the prior art. One of skill in the art would have been expected to have a reasonable expectation of success because the art teaches the successful

maker and use of such compositions. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant argues that Tomalia et al. and Meade et al. do not cure the deficiencies noted above. This is not found persuasive for the reasons set forth above.

Conclusion

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ileana Popa/
Primary Examiner, Art Unit 1633